REPLACED BY ART 34 AMDT

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.11.2004
Applicant's or agent's file reference AJC/P100596WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/02886	04.07.2003	05.07.2002

Applicant
UNIVERSITY OF LEEDS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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5/11/05
10/12/04

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AJC/P100596WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/02886	International filing date *(day/month/year)* 04.07.2003	Priority date *(day/month/year)* 05.07.2002
International Patent Classification (IPC) or both national classification and IPC C07F17/00		
Applicant UNIVERSITY OF LEEDS et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 10 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.02.2004	15.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Zellner, A Telephone No. +49 89 2399-8078

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02886

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1, 2, 8-11	as originally filed
3-7	received on 21.09.2004 with letter of 17.09.2004

Claims, Numbers

1-24	received on 21.09.2004 with letter of 17.09.2004

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-8, 21-24 (part)

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-8, 21-24 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24
	No:	Claims	
Inventive step (IS)	Yes:	Claims	13-20
	No:	Claims	1-12,21-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations

   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. The documents referred to in this report are numbered according to their appearance in the International Search Report; the numbering will be adhered to in the rest of the procedure.

2. The present application relates to metallocene compounds for use as a medicament in the treatment of cancer.

3. Amended claim 15 now claims for the HCl adduct of the compound claimed in original claim 15. A combination of a compound as originally disclosed in claim 15 and HCl does not appear to be disclosed in the application documents as filed since several different possible counter ions are mentioned. An unambiguous basis for the amendment is thus not disclosed, the amendment is **not allowable** with respect to Art. 43 (2)(b) PCT. The same applies for amended p. 6 of the description.

   The remaining amendments are considered allowable with respect to Art. 43 (2)(b) PCT.

item **III**

4. The International Search Report has not been established for the entire claimed subject-matter. This communication thus only relates to that part of the claims for which a search report has been established, i.e. those parts relating to compounds wherein L comprises an amino group (claims 1-8, 21-24 (part) and claims 9-20).

item **V**

5. Novelty (Art. 33(2) PCT)

   Document D1 discloses a compound of general formula 1 according to the present application (see p. 6, last paragraph). Although D1 mentions the potential use of compounds disclosed therein as anti-tumor agents it would appear that no clear teaching of that particular use is disclosed (p. 1, l. 19-27). Since all of the amended claims refer to the compounds for use as a medicament in the treatment of cancer, novelty can be acknowledged. The requirements of Art. 33(2) PCT are thus met.

6. Inventive step (Art. 33(3) PCT)

The applicant has set himself the task to provide water soluble metallocene compounds which are effective in the treatment of cancer. Compound 2 of the application appears to solve that technical problem.

Titanocene dichloride is a known agent for cancer treatment (D1, D2). It is also known that this compound is of limited use due to its low solubility and unstability in aqueous solutions (D1: p. 1, l. 22 ff; application p. 2, l. 18-23). Although it is known to enhance water-solubility by adding an amino group to one or both cp-groups (D1) it can be considered surprising that compound 2 of the present application is almost a factor 10 more active than Cp_2TiCl_2 (description, p. 8, l. 18-20). The presence of an inventive step can thus be acknowledged for the subject-matter directed to compound 2 for use in a medicament in the treatment of cancer.

Claim 1 on file, however, is not limited to subject-matter for which a surprising effect has credibly been shown but to a broader class of compounds which is, in addition, not clearly defined (see item 8 of this report). In applicant's letter dated 21.09.2004 it is stated that the subject-matter of D5 essentially differs from the application in that the compounds comprise covalent amino groups rather than groups which enable the compounds to become water-soluble. It would thus appear that the applicant does not consider compounds comprising covalent amino groups in the side chains as suitable for solving the technical problem, i.e. the provision of compounds having enhanced water-solubility. Claims 8-12, however, specifically refer to compounds comprising amino groups. The presence of an inventive step can thus not be acknowledged for the entire scope of claims 1-12 and 21-24 since it is not limited to compounds comprising quaternary ammonium groups. The present application does thus not fulfil the requirements of Art. 33(3) PCT.

7. Industrial applicability (Art. 33(4) PCT)

Can be acknowledged for claims the present claims 1-24.

item **VIII**

8. Present claim 1 does not fulfill the requirements of Art. 6 PCT. The claimed subject-matter is defined by the mere definition of the problem to be solved, i.e. to render metallocene compounds which can be used in the treatment of cancer more water-soluble.

It is noted that amended claims 13-20 claim for compounds comprising quaternary ammonium groups whereas claims 8-12 refer to compounds comprising amino groups, i.e. uncharged groups, which is also the case with compounds disclosed in document D5 (covalent amino groups in the side chains). Apparently the applicant considers both types of groups covered by the expression "a group which enables the compound to become water-solubilised" (in contrast to the reasoning with respect to document D5, see under point 6. inventive step of this report). The said expression is thus not considered suitable to define the claimed subject-matter (Art. 6 PCT).

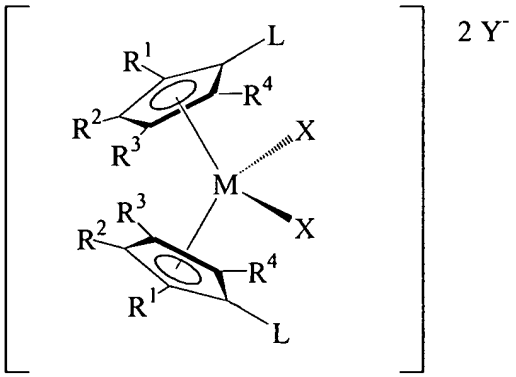
The present inventors, in the co-pending patent application published as WO 01/42260 have disclosed methods for the synthesis of metallocene halide salts having at least one cyclopentadiene group substituted by a basic group. However, that application contains no disclosure of the use of these materials for the treatment of cancer and, consequently, no data are provided for the success or otherwise of these materials in such treatments.

Most particularly, the present invention is concerned with various titanocene, vanadocene and molybdocene dichlorides, their synthesis and characterisation, and their use in the treatment of diseases, primarily cancer. The invention also involves an investigation of the efficiency of such compounds.

Thus, there are provided a number of water soluble metallocene halide salts, which have the potential to act as potent and effective anticancer agents. In addition, evidence is presented with regard to the increased stability and enhanced activity of these ionic metallocenes with respect to different sets of cancer cell lines.

STATEMENTS OF INVENTION

According to the present invention, there is provided a metallocene compound **1** for use as a medicament in the treatment of cancer.



1

In **1**: R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl;

L represents side chain substituents, at least one of which contains a group which enables the compound to become water-solubilised;

X is halo, alkoxy, acetate or H_2O;

Y is a counter-ion;

M is a metal; and

n = 1 or 2.

Specifically, the value of n is determined by the requirement for the molecule to show electrical neutrality and, consequently, is determined by the number of substituents L which contain a group which enables the compound to become water-solubilised. Thus, when the molecule contains one substituent L which enables the compound to become water-solubilised, n = 1 and, when the molecule contains two such groups, n = 2.

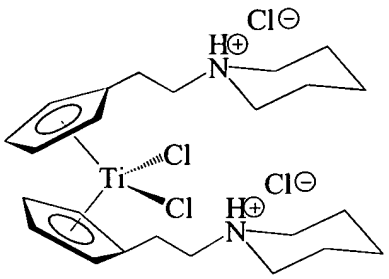
Preferably the metal is titanium, vanadium, niobium or molybdenum. Typical counter-ions include halide, acetate, tetrafluoroborate or hexafluorophosphate ions. The preferred titanocene, vanadocene niobiocene and molybdocene compounds are most preferably in the form of the dichloride salts. The compounds may be in the form of solvates or pro-drugs.

At least one cyclopentadienyl ring is functionalised by means of the group L such that the compound is water soluble. Preferably the at least one cyclopentadienyl ring is functionalised by a group L that carries a pendant Lewis base which confers aqueous solubility, such as an amino-functionalised side chain which can be quaternised.

Typically, in order to funtionalise the cyclopentadienyl ring, the group L comprises an alkyl group with a terminal Lewis base and preferably L has the formula

$$-(CH_2)_nZ$$

wherein n is an integer from 1 to 20 and Z comprises an amino group, for instance a secondary amino group, a particularly favoured example being a $-(CH_2)_2N(CH_2)_5$ group, which may be quaternised to provide compounds such as those of formula **2** or **3**. These compounds may comprise trialkyl ammonium halides, such as the compound of formula **2** or, most advantageously, novel tetraalkylammonium compounds including the compound of formula **3**.



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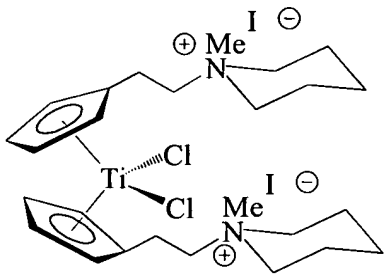

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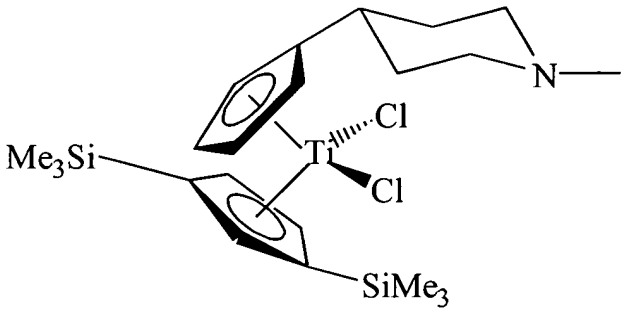
According to the invention, at least one of the L groups comprises a functionalised substituent capable of enabling the compound to become water-solubilised, and both groups may comprise such substituents. However, on the occasions when only one of the L groups comprises such a functionalised substituent,

then the L group on the other cyclopentadienyl ring may comprise any substituent not associated with conferring aqueous solubility on the molecule, typical examples being alkyl, aryl, aralkyl or, preferably, trialkylsilyl groups, for example, trimethylsilyl groups; alternatively, in such cases, L may be hydrogen.

Particular examples of compounds wherein only one of the L groups comprises a functionalised substituent include those of formulae **4**, **5**, **6** and **7**.



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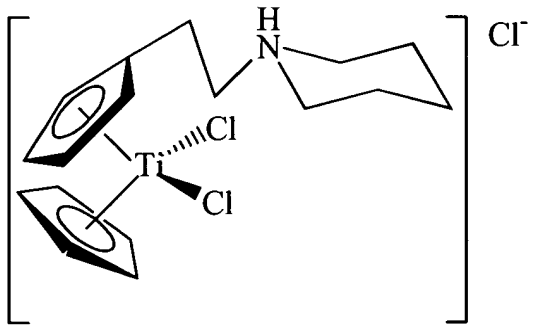

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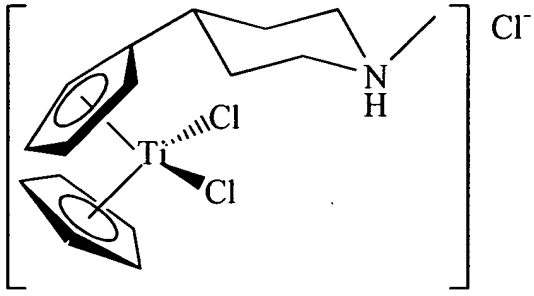

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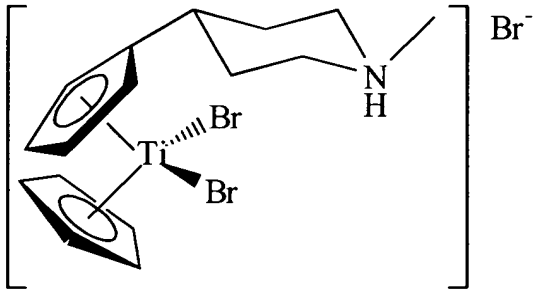

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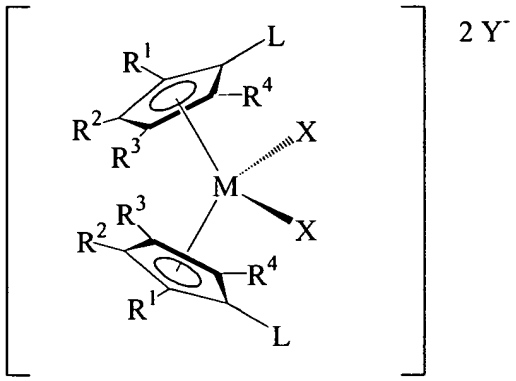
Specifically, the present invention relates to a series of compounds having an ionic feature which is contained within the ligand. This ionic character enables the compounds to overcome the problems of poor water solubility and instability to hydrolysis which are associated with the compounds of the prior art. Thus, the compounds are found to act as potent anti-tumour reagents.

The invention provides a method of treating and/or preventing cancer, which encompasses the administration of a therapeutically effective amount of the compounds **1** to the patient.

Administration of the compounds of invention comprises of a number of routes including orally, parenterally, topically, nasally or via slow releasing microcarriers.

CLAIMS

1. A metallocene compound of formula **1** for use as a medicament in the treatment of cancer.



1

wherein R^1, R^2, R^3 and R^4 represent a combination of H, alkyl, aryl or trimethylsilyl;

L represents side chain substituents, at least one of which contains a group which enables the compound to become water-solubilised;

X is halo, alkoxy, acetate or H_2O;

Y is a counter-ion;

M is a metal; and

n = 1 or 2,

wherein n = 1 when one of the side chain substituents L contains a group which enables the compound to become water-solubilised, and n = 2 when both of the side chain substituents L contain groups which enables the compound to become water-solubilised.

2. A metallocene compound as claimed in claim 1 wherein the metal M is titanium, vanadium, niobium or molybdenum.

3. A metallocene compound as claimed in claim 1 or 2 wherein the counter-ion Y is a halide, acetate, tetrafluoroborate or hexafluorophosphate ion.

4. A metallocene compound as claimed in claim 1, 2 or 3 which is in the form of the dichloride salt.

5. A metallocene compound as claimed in any one of claims 1 to 4 which is in the form of a solvate or a pro-drug.

6. A metallocene compound as claimed in any preceding claim wherein both groups L are functionalised to enable the compound to become water-solubilised.

7. A metallocene compound as claimed in any preceding claim wherein only one group L is functionalised to enable the compound to become water-solubilised.

8. A metallocene compound as claimed in any preceding claim wherein L comprises a group which carries a pendant Lewis base.

9. A metallocene compound as claimed in claim 8 wherein the Lewis base is provided by an amino group.

10. A metallocene compound as claimed in claim 9 wherein the amino group is a secondary amino group.

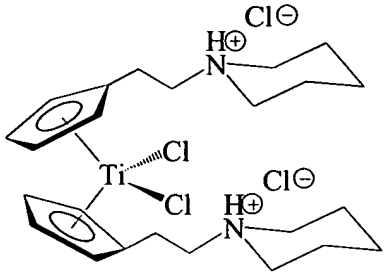
11. A metallocene compound as claimed in claim 10 wherein the secondary amino group comprises a $-(CH_2)_2N(CH_2)_5$ group.

12. A metallocene compound as claimed in claim 9 wherein the group L has the formula

$$-(CH_2)_nZ$$

wherein n is an integer from 1 to 20 and Z comprises an amino group.

13. A metallocene compound as claimed in claim 1 which has the formula **2**:



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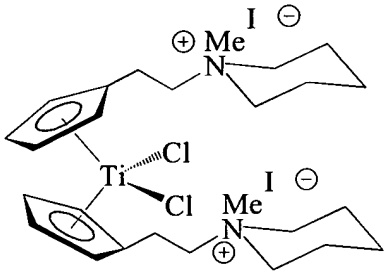
14. A metallocene compound as claimed in claim 1 which has the formula **3**:



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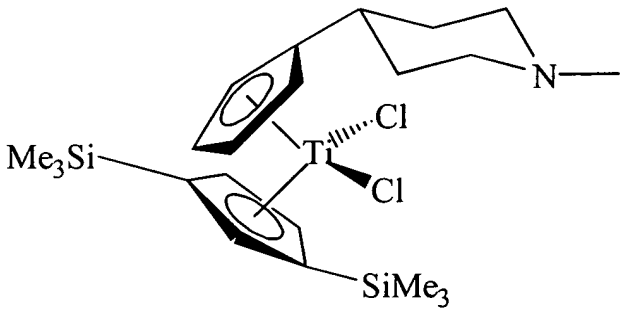
15. A metallocene compound as claimed in claim 1 which has the formula **4**:



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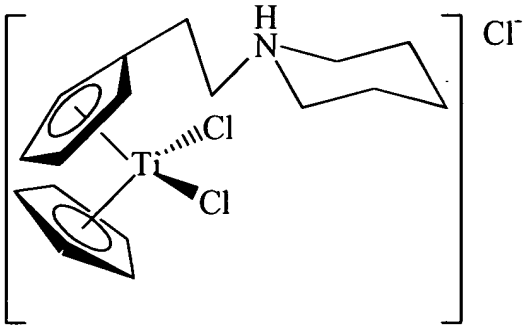
16. A metallocene compound as claimed in claim 1 which has the formula **5**:



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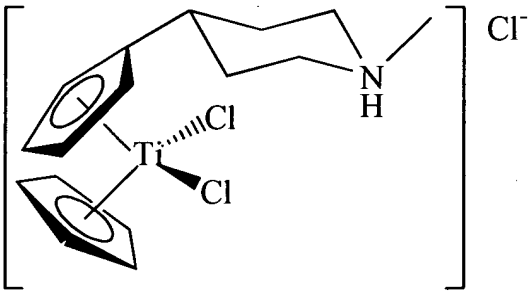
17. A metallocene compound as claimed in claim 1 which has the formula **6**:



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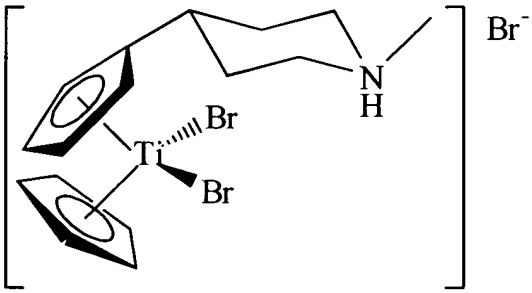
18. A metallocene compound as claimed in claim 1 which has the formula **7**:



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19. A metallocene compound as claimed in any one of claims 1 to 18 wherein both groups L comprise a quaternary tetraalkylammonium group.

20. A metallocene compound as claimed in any one of claims 1 to 18 wherein only one group L comprises quaternary tetraalkylammonium group.

21. A metallocene compound as claimed in any one of claims 1 to 20 for administration to a patient orally, parenterally, topically, nasally or via slow releasing microcarriers.

22. A metallocene compound as claimed in any one of claims 1 to 21 wherein excipients comprise saline, sterile water, creams, ointments, solutions, gels, pastes, emulsions, lotions, oils, solid carriers or aerosols.

23. A metallocene compound as claimed in any one of claims 1 to 22 for administration alone or in combination with at least one other compound.

24. A metallocene compound as claimed in claim 23 wherein said at least one other compound has biological activity.